The Potential Role of Direct Thrombin Inhibitors in the Prevention and Treatment of Venous Thromboembolism*

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Venous thromboembolism (VTE) is a common and potentially lethal disease that recurs frequently and is associated with long-term impairment and suffering. Despite a great deal of effort, the incidence of VTE has not changed substantially in the last 20 years. Independent risk factors include hospitalization (either for surgery or for acute medical illness), trauma, malignant neoplasm, central venous catheters or transvenous pacemakers, superficial vein thrombosis, and extremity paresis. Of these, hospitalization accounts for almost 60% of all VTE occurring in the community. Thus, universal effective prophylaxis of hospitalized patients would significantly reduce the incidence of VTE. Parenteral direct thrombin inhibitors are safe and effective for both prevention and treatment of acute VTE, and do not require laboratory monitoring or dose adjustment. Oral direct thrombin inhibitors may also be safe and effective, and offer enhanced convenience without diet or drug-drug interactions.

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Key words: deep vein thrombosis; prophylaxis; pulmonary embolism; treatment; thrombin venous thromboembolism

Abbreviations: CI = confidence interval; DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SC = subcutaneous; UFH = unfractionated heparin; VTE = venous thromboembolism

Venous thromboembolism (VTE) mainly consists of deep vein thrombosis (DVT) and its complication, pulmonary embolism (PE). VTE is a common disease, with an average annual incidence of > 1 per 1,000 person-years.[1] VTE is also a lethal disease, mostly due to PE. Almost one third of all patients with PE die within 7 days, and one fourth die suddenly (Table 1).[2] For the latter patients, available time is insufficient to recognize, diagnose, and begin therapy in order to alter the course of the disease. Compared to DVT, PE is an independent predictor of reduced survival for up to 3 months.[3] Thus, PE is a frequent cause of death independent of other comorbidities (*eg*, cancer, congestive heart failure, stroke, etc). Although most patients survive DVT, they often have other serious and costly long-term complications. Almost 30% acquire serious venous stasis syndrome (manifest as painful swelling and recurrent ulcers of the affected leg) within 10 years[3,4] at an estimated cost of > $4,000 per episode in 1997 US dollars.[5] Thus, VTE is a major health-care problem.

VTE Epidemiology

In order to improve survival, prevent complications, and reduce health-care costs, the occurrence of VTE must be reduced. However, the incidence of VTE has remained relatively constant since about 1980 (Fig 1).[1,6] The failure to reduce VTE incidence may reflect an increase in the population at risk (*eg*, an increase in the average population age), exposure of the population to more or new risk factors (*eg*, an increase in surgical procedures),[7] inadequate identification of all high-risk populations, underutilization of appropriate prophylaxis,[8,9] or prophylaxis failure.

Provision of appropriate prophylaxis requires that persons at risk for VTE be identified. The effect of patient age must always be included in any estimate of VTE risk. VTE incidence increases markedly with age for both men and women (Fig 2).[1] Moreover, the relative proportion presenting as PE (with its associated poor survival) also increases with age (Fig 3).[1] Thus, as the average US population age increases, the incidence of PE also will increase. Independent risk factors for VTE include confinement to a hospital (with or without surgery) or nursing home, trauma, malignant neoplasm (with or without chemotherapy), central venous catheterization or placement of a transvenous pacemaker, prior superficial vein thrombosis, and serious neurologic disease with extremity paresis (Table 2).[10] Among women, additional risk factors for VTE include pregnancy and the postpartum period,[11] oral contraceptive use,[12] hormone replacement therapy,[13] and selective estrogen receptor modulator therapy (*eg*, tamoxifen, raloxifene). Other conditions associated with VTE include heparin-induced thrombocytopenia and thrombosis, myeloproliferative disorders, intravascular coagulation and fibrinolysis/disseminated intravascular coagulation, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, thromboangiitis obliterans (Buerger disease), thrombotic thrombocytopenic purpura, Bechet syndrome, systemic lupus erythematosus, and inflammatory bowel disease.

Of all independent risk factors for VTE, hospitalization for surgery or medical illness conveys the highest risk.[10] The incidence of VTE is > 150-fold higher among hospitalized patients compared to community residents.[8] Hospitalization accounts for almost half of all VTE in the community (Table 3).[14] Thus, appropriate prophylaxis of the hospitalized patient provides an opportunity to significantly reduce the incidence of VTE.

VTE also recurs frequently, with an overall cumulative

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Table 1—*Survival After VTE**

Time	DVT Alone	PE With or Without DVT	All VTE
0 d	97.0	76.5	77.7
7 d	96.2	71.1	74.8
14 d	95.7	68.7	73.3
30 d	94.5	66.8	72.0
90 d	91.9	62.8	68.9
1 yr	85.4	57.4	63.6
2 yr	81.4	53.6	60.1
5 yr	72.6	47.4	53.5
8 yr	65.2	41.5	47.5

*From Heit et al.[2] Data are presented as %.

recurrence of 30% by 10 years (Fig 4).[15] However, the hazard of recurrence varies according to the duration of time since the incident venous thromboembolic event. For example, the hazard is highest in the first 6 to 12 months, ranging from 170 recurrent events per 1,000 person-days at 7 days, to 130 events at 90 days and 20 events at 1 year (Fig 4). Importantly, the hazard of recurrence never falls to zero, continuing at 10 recurrent events per 1,000 person-days at 2 years, 6 events at 5 years, and 5 events at 10 years. Thus, VTE should be viewed as a chronic disease with episodic recurrence. For those patients whose recurrence is manifest as PE, the 7-day case fatality is 31%.[16] If the recurrence is manifest as DVT, the risk of subsequent venous stasis syndrome is increased over sixfold, with a cumulative incidence of 28% by 5 years.[17,18] Identifying patients at increased risk for VTE recurrence is important since secondary prophylaxis (*eg*, long-term anticoagulation therapy) is very effective in preventing recurrence.[19,20] Independent predictors of VTE recurrence include increasing age and body mass index, malignant neoplasm (with or without chemotherapy), and neurologic disease with paresis (Table 4).[15] Additional predictors of recurrence include unprovoked ("idiopathic") VTE,[20,21] a lupus anticoagulant or antiphospholipid antibody,[20,22] and either homozygosity for the factor V Leiden mutation or combined heterozygosity for both the factor V Leiden and prothrombin nucleotide 20210G→A mutations.[23] For women, pregnancy or the postpartum state, oral contraceptive use, and gynecologic surgery are associated with a reduced risk of recurrence.[15] Additional transient baseline characteristics that have no significant effect on recurrence risk include the incident event type (DVT vs PE), anticoagulation prophylaxis immediately preceding or at the time of the incident event, immobilization, general surgery, orthopedic surgery, trauma, fracture, hormone therapy, and tamoxifen therapy.[15]

VTE Pathogenesis

The pathogenesis of venous thrombosis is poorly understood. Venous thrombosis likely reflects an abnormality in the normal reparative response to venous endothelial injury. This hypothesis suggests that venous thrombosis occurs when there is a breakdown in the mechanisms that localize or constrain a normal hemostatic thrombus to the site of vein injury. The unconstrained thrombus enlarges by continued clot accretion, eventually leading to vein occlusion and/or thrombus embolization.

The most likely cause of venous endothelial injury is direct trauma through vein torsion, compression, or overdilation. Electron microscopy studies have demonstrated endothelial "microtears" due to venodilation.[24] The events following venous injury are less clear. Animal model data suggest that the earliest events are platelet adhesion to adjacent venous endothelial cell junctions or exposed subendothelial matrix.[25] However, while platelets likely are necessary in the pathogenesis of venous thrombosis, platelet adhesion and cohesion alone (as in arterial throm-

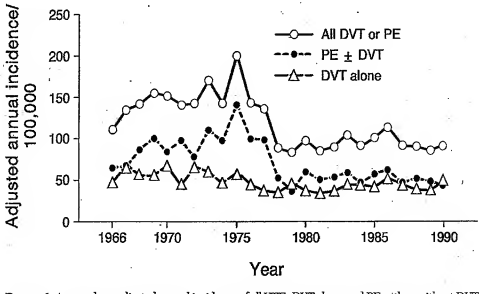

FIGURE 1. Age- and sex-adjusted annual incidence of all VTE, DVT alone, and PE with or without DVT among Olmsted County, MN residents, by calendar year, from 1966 to 1990.[1]

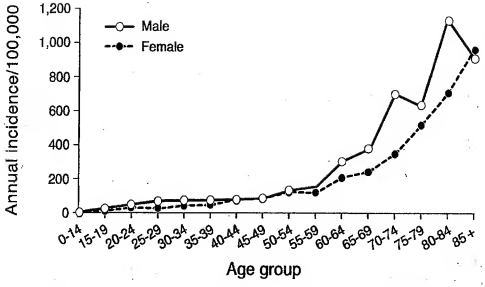

FIGURE 2. Annual incidence of VTE among Olmsted County, MN residents, from 1966 to 1990, by age and gender.[1]

bosis) are insufficient. Venous thrombosis frequently occurs despite profound thrombocytopenia (eg, cancer patients receiving chemotherapy). Moreover, platelet inhibition (at least by aspirin) provides minimal if any protection against VTE after surgery.[26] Activation of the procoagulant system, by exposure or by expression of tissue factor,[27,28] and generation of thrombin are necessary in the pathogenesis of venous thrombosis. In support of tissue factor as at least one initiator of venous thrombosis, inhibition of the tissue factor-factor VIIa complex has been proven effective as prophylaxis against postoperative VTE.[29] The central role of thrombin in the pathogenesis of venous thrombosis is shown by the abundant clinical trial data demonstrating the efficacy of direct or indirect thrombin inhibition (or factor Xa inhibition) as primary and secondary VTE prophylaxis.[20,21,26]

Forces opposing the initiation and growth of a venous thrombus include the anticoagulant (protein C/thrombomodulin, protein S, antithrombin) and fibrinolytic systems.[30] The plasma "acute-phase" response to injury acts to inhibit both of these systems. The acute-phase response is mediated by lymphocytokines (eg, interleukin-1, tumor necrosis factor-α)[31] and includes increases in procoagulant factor levels (fibrinogen, factor VIII, and von Willebrand

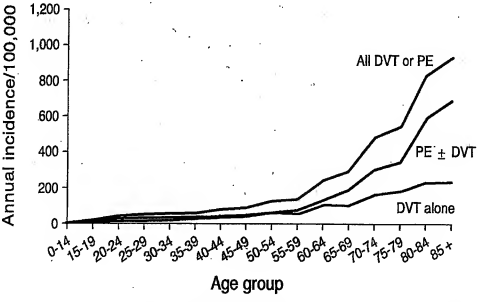

FIGURE 3. Annual incidence of all VTE, DVT alone, and PE with or without DVT among Olmsted County, MN residents, from 1966 to 1990, by age.[1]

Table 2—*Independent Risk Factors for DVT or PE**

Baseline Characteristics	Odds Ratio	95% CI
Hospitalization with recent surgery	21.72	9.44–49.93
Hospitalization without recent surgery	7.98	4.49–14.18
Trauma	12.69	4.06–39.66
Malignancy without chemotherapy	4.05	1.93–8.52
Malignancy with chemotherapy	6.53	2.11–20.23
Prior central venous catheter or transvenous pacemaker	5.55	1.57–19.58
Prior superficial vein thrombosis	4.32	1.76–10.61
Neurologic disease with extremity paresis	3.04	1.25–7.38
Serious liver disease	0.10	0.01–0.71

*From Heit et al.[10]

Table 3—*Population-Attributable Risk Associated With Independent Risk Factors for VTE**

Risk Factors	Attributable Risk, %†	95% CI
Hospitalization or nursing home	58.8	53.4–64.2
Hospitalization with surgery	23.8	20.3–27.3
Hospitalization without surgery	21.5	17.3–25.6
Nursing home	13.3	9.9–16.8
Active malignant neoplasm	18.0	13.4–22.6
Malignant neoplasm with chemotherapy	6.4	3.9–9.0
Malignant neoplasm without chemotherapy	11.6	7.6–15.5
Trauma	12.0	9.0–14.92
Congestive heart failure	9.5	3.3–15.8
Prior central venous catheter or pacemaker	9.1	5.7–12.6
Neurologic disease with extremity paresis	6.9	3.5–10.2
Prior superficial vein thrombosis	5.4	3.0–7.7

*From Heit et al.[14]
†Adjusted for age, sex, year of event, and terms in final model.

factor),[32] increased plasminogen activator inhibitor-1,[33] which indirectly inhibits the fibrinolytic system,[34] and decreased antithrombin.[35] Based on cell culture experiments, cytokine-induced expression of tissue factor[36] and endocytosis of thrombomodulin on the endothelial cell surface[37] may act in concert to increase thrombin levels. Expression of endothelial cell-surface receptors promotes the adhesion and emigration of leukocytes that contribute to local inflammation.[38,39] Taken together, these factors may promote both the continued growth and reduced clearance of a normal hemostatic thrombus at the site of local venous injury.

Direct Thrombin Inhibitors for the Prevention and Treatment of VTE

A complete review of the prevention and treatment of VTE is beyond the scope of this review and has been recently discussed in detail elsewhere.[25,40] This review focuses on the role of the direct thrombin inhibitors recombinant hirudin (desirudin, lepirudin), hirulog (bivalirudin), argatroban, melagatran/ximelagatran, and dabigatran (BIBR-953)/BIBR-1048 in VTE prophylaxis and treatment.

Pharmacology of Direct Thrombin Inhibitors

Hirudin, the prototypical direct thrombin inhibitor, was originally isolated from the medicinal leech, *Hirudo medicinalis*. Hirudin is a 65-amino acid polypeptide that binds thrombin with high affinity at both the thrombin active site and exosite 1, forming a 1:1 stoichiometric complex. Recombinant hirudin lacks a sulfate group on tyrosine 63, and thus has been termed desulfatohirudin (*eg*, desirudin). Native and desulfatohirudin must be administered parenterally. The plasma half-life is approximately 1 h, and body elimination is via renal excretion. Hirulog (bivalirudin), a 20-amino acid polypeptide modeled after hirudin, consists of an aminoterminal D-Phe-Pro-Arg-Pro domain that interacts with the thrombin-active site, a linker region of four glycines, and a dodecapeptide analog of the hirudin carboxy-terminus that binds thrombin exosite 1.[41] Bivalirudin also must be administered parenterally, with a plasma half-life of 25 min. Elimination is via degradation by endogenous peptidases. Argatroban is a synthetic, arginine-derivative, small molecule that interacts only with the thrombin-active site.[42] Argatroban is administered parenterally and is metabolized in the liver, with a plasma half-life of 45 min. Melagatran is a dipeptide mimetic of the fibrinopeptide A region that interacts with the thrombin-active site. Melagatran requires parenteral administration. Ximelagatran is a prodrug of melagatran that is well absorbed after oral administration and has no food or drug interactions. After absorption, ximelagatran is rapidly converted to melagatran, with a plasma half-life of approximately 3 h.[43,44] Melagatran is primarily eliminated by renal excretion. BIBR-1048 is an oral prodrug that is converted to dabigatran (BIBR-953), a potent nonpeptide benzamidine-based thrombin inhibitor.[45] The plasma half-life of dabigatran is 14 to 17 h, and elimination is also primarily by renal excretion.[45,47]

Direct Thrombin Inhibitors as VTE Prophylaxis After Surgery

Recombinant hirudin, hirulog, melagatran/ximelagatran, and ximelagatran alone have been tested as VTE prophylaxis after elective total hip or knee replacement surgery. All studies used symptomatic VTE or asymptomatic DVT as detected by venography as the study end point. In addition, recombinant hirudin, hirulog, melagatran, ximelagatran, and low-molecular-weight heparin (LMWH) were administered as fixed doses (*eg*, non-weight adjusted) and without laboratory monitoring of anticoagulant effect or dose adjustment. There are no adequate clinical trials testing argatroban as VTE prophylaxis.

In a phase II dose-finding study, patients undergoing elective total hip replacement (n = 1,119) were randomly assigned to one of three doses of recombinant hirudin (desirudin, 10 mg, 15 mg, or 20 mg subcutaneous [SC] bid, initiated preoperatively) or unfractionated heparin

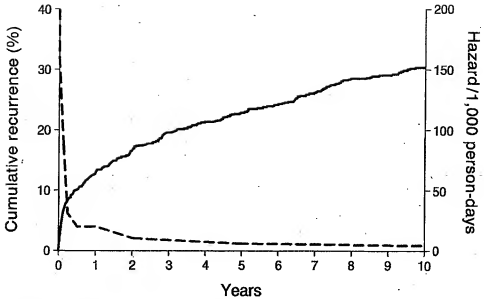

FIGURE 4. Cumulative incidence of first VTE recurrence (—), and the hazard of first recurrence per 1,000 person-days (- - -).

(UFH), 5,000 U SC q8h (Table 5).[48] All doses of desirudin were significantly more effective than UFH in preventing both overall VTE (*eg*, symptomatic VTE and asymptomatic proximal and/or distal DVT detected by venography) and proximal DVT. However, total blood loss was significantly greater for the hirudin, 20 mg bid, dose. Thus, the two subsequent phase III trials tested only the desirudin, 15 mg bid, dose. In the first phase III trial, total hip replacement patients (n = 445) were randomized to either desirudin or UFH at 5,000 U SC tid.[49] Again, both the overall VTE and proximal DVT rates were significantly less in the desirudin group. While there were no significant differences between the two groups in blood loss, transfusion requirements, or bleeding complications, two patients receiving UFH prophylaxis acquired severe heparin-induced thrombocytopenia (one case was fatal). In the final study, 1,587 patients receiving total hip replacement were randomized to desirudin or enoxaparin sodium at 40 mg SC qd.[50] The overall VTE and proximal DVT rates were significantly lower for desirudin compared to enoxaparin. The two groups did not differ significantly with respect to blood loss, transfusion requirements, or serious bleeding.

Table 4—*Independent Predictors of VTE Recurrence**

Characteristics	Hazard Ratio	95% CI
Age†	1.17	1.11–1.24
Body mass index‡	1.24	1.04–1.47
Neurologic disease with extremity paresis	1.87	1.28–2.73
Malignancy with chemotherapy	4.24	2.58–6.95
Malignancy without chemotherapy	2.21	1.60–3.06

*From Heit et al.[15]
†Per decade increase in age.
‡Per 10 kg/m^2 increase in body mass index.

Hirulog has been tested as prophylaxis after major hip or knee surgery in one small phase II dose-finding study[51] involving 177 patients (Table 5), which study tested five hirulog subcutaneous doses (0.3 mg/kg q12h, 0.6 mg/kg q12h, 1.0 mg/kg q12h for 3 days followed by 0.6 mg/kg q12h for up to 11 days, 1.0 mg/kg q12h, or 1.0 mg/kg q8h), and did not include a comparator study arm. The highest hirulog dose regimen tested was associated with a 17% overall (2% proximal) DVT rate. Bleeding rates were low with all doses tested.

Melagatran and/or ximelagatran have been compared with either LMWH or warfarin prophylaxis in a series of clinical trials (Table 6). In an initial phase II dose-finding study,[52] 443 adults undergoing total knee replacement were randomly assigned to receive oral ximelagatran twice daily in blinded doses of 8 mg, 12 mg, 18 mg, or 24 mg, or open-label enoxaparin sodium at 30 mg SC bid. Both were started 12 to 24 h after surgery and continued for 6 to 12 days. The rates of overall VTE and proximal DVT or PE for ximelagatran, 24 mg, vs enoxaparin did not differ significantly. There was no major bleeding with ximelagatran at 24 mg bid. In a follow-on phase III double-blind clinical trial,[53] 1,838 patients undergoing elective total hip replacement were randomly assigned to prophylaxis with oral ximelagatran at 24 mg bid or enoxaparin sodium at 30 mg SC bid. Both drugs were started on the morning after surgery. Both the overall VTE and proximal DVT or PE rates were higher for ximelagatran at 24 mg vs enoxaparin, while the major bleeding rates were low and did not differ significantly.

Three Scandinavian studies compared the combination of melagatran and ximelagatran vs LMWH as prophylaxis after total hip or knee replacement. In a small initial dose-finding study,[54] 135 total hip or knee replacement patients were randomly allocated to melagatran (1 mg, 2 mg, or 4 mg SC bid, started immediately before surgery)

Table 5—*Recombinant Hirudin and Hirulog in the Prevention of VTE*

Source/Surgery	Variables	Thrombin Inhibitor Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Heparin
Eriksson et al[48]/total hip replacement	Hirudin dose (bid)	10 mg	15 mg	20 mg			UFH 5,000 U tid
	Overall VTE, %	23.3	18.8	18.3			33.6
(n = 1,119)	Proximal VTE, %	8.5	3.1	2.4			19.6
Eriksson et al[49]/total hip replacement	Hirudin dose (bid)	15 mg					UFH 5,000 U tid
	Overall VTE, %	7					23
(n = 445)	Proximal VTE, %	3					16
Eriksson et al[50]/total hip replacement	Hirudin dose (bid)	15 mg					Enoxaparin 40 mg
	Overall VTE, %	18.4					25.5
(n = 2,079)	Proximal VTE, %	4.5					7.5
	Serious bleeding	1.9					2.0
Ginsburg et al[51]/major hip or knee surgery	Hirulog dose, mg/kg q12h	0.3	0.6	1.0 for 3 d, then 0.6	1.0	1.0 q8h	
(n = 177)	Overall VTE, %	59	40	40	35	17	
	Proximal VTE, %	41	17	15	20	2	

for 2 days, followed by oral ximelagatran (6 mg, 12 mg, or 24 mg bid) for 6 to 9 days, or to dalteparin sodium at 5,000 IU SC qd (started the night before surgery). Including all melagatran/ximelagatran prophylaxis study arms, the overall VTE rate was 18.5% compared to 20.5% for the dalteparin study arm. In a much larger phase II dose-finding study, 1,900 patients were randomly assigned to one of four melagatran/ximelagatran doses: 1.00 mg/8 mg, 1.50 mg/12 mg, 2.25 mg/18 mg, or 3.00 mg/24 mg.[55] The first melagatran dose was injected SC immediately before surgery but after administration of neuraxial (spinal or epidural) anesthesia. A second melagatran injection was administered 7 to 11 h after surgery, followed by twice-daily injections until oral ximelagatran could be started (usually 1 to 3 days after surgery). A highly significant dose-dependent decrease in VTE (both overall and for proximal DVT) was seen with increasing doses of melagatran/ximelagatran.

In a subsequent phase III study,[56] 2,764 patients undergoing elective total hip or knee replacement were randomly assigned to prophylaxis with melagatran/ximelagatran or enoxaparin sodium. Melagatran, 2 mg SC, was administered immediately before surgery and again (3 mg SC) on the evening of surgery, followed by oral ximelagatran, 24 mg bid. Enoxaparin, 40 mg SC, was started on the evening before surgery and continued daily thereafter starting on the day after surgery. The overall VTE and proximal DVT rates were significantly less in the melagatran/ximelagatran group compared to the enoxaparin group. While bleeding events (3.3% vs 1.2%) and transfusion rates (66.8% vs 61.7%) were more common in the melagatran/ximelagatran group compared to the enoxaparin group, there were no significant differences between the two groups in fatal bleeding, critical organ bleeding, or bleeding requiring reoperation.

Two clinical trials compared ximelagatran to adjusted-

Table 6—*Melagatran/Ximelagatran vs LMWH in the Prevention of VTE*

Source/Surgery	Variables	Thrombin Inhibitor Dose 1	Dose 2	Dose 3	Dose 4	LMWH
Heit et al[52]/total knee	Ximelagatran dose, mg	8	12	18	24	Enoxaparin, 30 mg bid
replacement (n = 443)	Overall VTE, %	27.0	19.8	28.7	15.8	22.7
	Proximal VTE, %	6.6	2.0	5.8	3.2	3.1
	Major bleeding, %	0	0	2.4	0	0.8
Colwell et al[53]/total knee	Ximelagatran dose, mg	24				Enoxaparin, 30 mg bid
replacement (n = 1,838)	Overall VTE, %	7.9				4.6
	Proximal VTE, %	3.6				1.2
	Major bleeding, %	0.8				0.9
Eriksson et al[54]/total hip or	Melagatran/ximelagatran dose, mg*	1/8	1.5/12	2.25/18	3/24	Dalteparin, 5,000 IU qd
total knee replacement	Overall VTE, %	37.8	24.1	23.7	15.1	28.2
(n = 1,900)	Proximal VTE, %	8.5	6.2	3.3	2.1	5.5
	Major bleeding, %	0.8	1.2	3.5	5.5	2.3
Eriksson et al[56]/total hip or	Ximelagatran dose, mg†	24				Enoxaparin, 40 mg qd
total knee replacement	Overall VTE, %	20.3				26.7
(n = 2,764)	Proximal VTE, %	2.3				6.3
	Major bleeding, %	3.3				1.2

*Melagatran SC followed by ximelagatran.
†Dose of ximelagatran was preceded by melagatran, 5 mg SC.

Table 7—*Ximelagatran vs Warfarin Sodium in the Prevention of VTE*

Source/Surgery	Variables	Ximelagatran		Warfarin
		Dose 1	Dose 2	
Francis et al[57]/total knee replacement (n = 680)	Dose, mg	24 bid		INR, 2.5; range, 1.8 to 3.0
	Overall VTE, %	19.2		25.7
	Proximal VTE, %	3.3		5.2
	Major bleeding, %	1.7		0.9
Francis et al[58]/total knee replacement (n = 2,301)	Dose, mg	24 bid	36 bid	INR, 2.5; range, 1.8 to 3.0
	Overall VTE, %	24.9	20.3	27.6
	Proximal VTE, %	2.5	2.7	4.1
	Major bleeding, %	4.8	5.3	4.5

dose warfarin sodium prophylaxis (Table 7). In a double-blind clinical trial,[57] 680 patients undergoing elective total knee replacement were randomly assigned to oral ximelagatran (24 mg bid, started on the morning after surgery) or adjusted-dose warfarin (international normalized ratio [INR], 2.5; range, 1.8 to 3.0; started on the evening after surgery). The overall VTE rates did not differ significantly between the ximelagatran and warfarin groups (19.2% vs 25.7%, $p = 0.07$). Similarly, the proximal VTE rates also did not differ significantly (3.3% vs 5.0%, $p > 0.2$). The rates of major and minor bleeding were low and not significantly different. In the second trial,[58] 2,301 patients undergoing total knee replacement were randomly assigned to prophylaxis with oral ximelagatran (24 mg or 36 mg bid, started the morning after surgery) or adjusted-dose warfarin (target INR, 2.5; range, 1.8 to 3.0; started the evening after surgery). The rates of overall VTE or death were significantly less among the ximelagatran, 36 mg, group compared to the warfarin group ($p = 0.003$ for the ximelagatran, 36 mg, vs warfarin comparison). The rates for proximal DVT or death were not significantly different. The rates of major and minor bleeding were low and did not differ significantly between the three groups.

The new oral direct thrombin inhibitor, BIBR-1048, has been tested in an open-label, dose-escalation, safety study among patients undergoing elective total hip replacement (n = 289).[59] BIBR-1048 (12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 20 mg bid, or 150 mg and 300 mg qd) was started 4 h after surgery and continued for 6 to 10 days. A dose response was demonstrated for peak and trough plasma levels as well as all bleeding events. While no major bleeding occurred, multisite bleeding was observed at the highest dose in two patients with reduced creatinine clearance and correspondingly high trough plasma drug levels. Further exploration of the safety dose range will be necessary.

Direct Thrombin Inhibitors as Treatment for Acute VTE

Only one study[60] has tested recombinant hirudin as treatment for acute VTE; in a phase II trial, 155 patients with DVT were randomly allocated to one of three hirudin doses (0.75 mg/kg, 1.25 mg/kg, or 2.00 mg/kg SC bid), or to adjusted-dose IV UFH. All patients received a baseline venogram and ventilation/perfusion lung scan. After 5 days of treatment, the venogram and lung scan were repeated for comparison. The rates of DVT progression, regression, or no change; the rate of new ventilation/perfusion mismatch; and the rates of adverse events did not differ between the four groups. While not approved for treatment of acute VTE, recombinant hirudin (lepirudin) and argatroban are US Food and Drug Administration approved for treatment of heparin-induced thrombocytopenia (HIT), which often manifests as acute VTE (*eg*, HIT and thrombosis).[61] In this circumstance, lepirudin would be the preferred treatment for HIT patients with impaired liver function, while argatroban would be preferred for HIT patients with impaired renal function. Hirulog has not been studied as VTE therapy.

A series of clinical trials have tested ximelagatran as treatment for acute VTE. Similar to the prophylaxis trials, ximelagatran was administered as a fixed oral dose and without laboratory monitoring of the anticoagulant effect or dose adjustment. Two initial studies used thrombus regression/progression or new embolism as study endpoints. In an initial dose-finding study,[62] 350 patients with acute proximal or extensive isolated distal (length > 7 cm) DVT confirmed by venography were randomly assigned to one of four oral ximelagatran doses (24 mg, 36 mg, 48 mg, or 60 mg bid), or to dalteparin sodium (200 IU/kg SC qd) followed by adjusted-dose warfarin (INR range, 2.0 to 3.0). Venography was repeated after 14 days of therapy, and the extent of each thrombus was quantified according to progression or regression of thrombus size and the Marder score. Regression of thrombus size was noted in 69% of both treatment groups, while thrombus progression was noted in 8% of ximelagatran and 3% of dalteparin/warfarin patients. Changes in Marder score also were similar in both groups. Therapy was discontinued due to bleeding in two patients in each group. In an open-label cohort study, 12 patients with PE verified by ventilation/perfusion lung scan (with or without DVT) were treated with oral ximelagatran, 48 mg bid, for 6 to 9 days, followed by conventional heparin and warfarin therapy.[63] All patients improved clinically. Repeat lung scans after completing ximelagatran showed regression or no change in all but one patient with malignancy; five patients had essentially normal perfusion scan findings. There were no major bleeding episodes or deaths.

In a novel, double-blind, clinical trial,[64] 1,233 patients with VTE who had completed 6 months of standard anticoagulation therapy were subsequently randomized to

continued secondary prophylaxis with oral ximelagatran, 24 mg bid, or placebo for an additional 18 months. Among the 612 patients receiving ximelagatran, 12 acquired recurrent VTE. In contrast, 71 of the 611 patients receiving placebo acquired recurrent VTE (hazard ratio, 0.16; 95% confidence interval [CI], 0.09 to 0.30; $p < 0.001$). The all-cause mortality and major and minor bleeding rates did not differ significantly between the two groups. Ximelagatran patients were more likely to have transient and generally asymptomatic increases (more than threefold the upper normal limit) in serum alanine aminotransferase compared to placebo (6.4% vs 1.2%).

In summary, VTE is a common, potentially lethal disease that recurs frequently and is associated with long-term impairment and suffering as well as substantial costs due to health-care charges and lost earnings. Despite a great deal of effort, the incidence of VTE has not changed substantially in the last 20 years. Parenteral direct thrombin inhibitors are safe and effective for both prevention and treatment of acute VTE, and do not require laboratory monitoring or dose adjustment. Oral direct thrombin inhibitors may also be safe and effective, and offer enhanced convenience without diet or drug-drug interactions.

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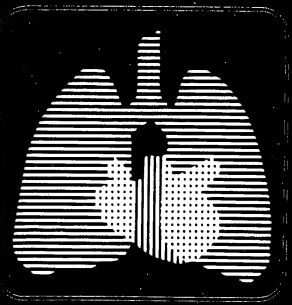

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